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IMPROVEMENTS IN OR RELATING TO CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS

Abstract:

Abstract of GB1278816

1278816 Controlled-release medicaments G S BANKER 2 Sept 1969 [3 Sept 1968] 43479/69 Heading A5B [Also in Division C3] Orally administrable sustained release compositions comprise a drug having an acid or basic functionality and a physiologically harmless carboxylic acid chemisorbed on the particles of a latex of a polymer containing acidic and/or basic groups the functionality of which is complementary to that of the drug and which is hydratable (at least to the extent that it swells) in the gastrointestinal tract. Suitable polymers are those formed by the emulsion polymerisation of such monomers as acrylic, methacrylic, crotonic, itaconic and maleic acids, half esters of maleic acid, maleic anhydride, sulphonated and phosphonated styrene, vinylamine and aminoalkyl esters of the above acids. Copolymerizates thereof, e.g. with vinyl compounds, acrylates, methacrylates and acrylonitrile may also be employed. The acid may be a mono- or polycarboxylic acid e.g. acetic acid, glycine, oxalic, malonic, succinic, glutaric, adipic, maleic, fumaric, citric or tartaric acid and numerous drugs and drug types are mentioned. The compositions may be made by adding solutions of the drug and acid to an emulsion (latex) of the resin. The product may be used as such in a liquid preparation or the resin may be separated e.g. by filtration, centrifugation, spray-drying &c either with or without initial flocculation as by addition of an electrolyte. Specific examples relate to preparations in which the drugs are methapyrilene, chlorpheniramine, phenylephrine, phenylpropanolamine, pyrilamine, atropine and oxytetracycline (all as salts) and phenobarbital, the resins being anionic acrylic copolymers and styrene-acrylic nonionic polymer. A different drug or some of the same drug may be present in the particles which is not chemisorbed but is merely physically entrapped. Data supplied from the esp@cenet database - Worldwide

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(54) IMPROVEMENTS IN OR RELATING TO CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS

(71) I, GILBERT STEVEN BANKER, a citizen of the United States of America, of School of Pharmacy, Purdue University, Lafayette, Indiana 47907, United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to controlled release pharmaceutical compositions for example to compositions having sustained release, enteric or delayed release properties, and to methods of preparation of these compositions. By controlled release the rate of dissolution and availability of the drug, that is to say the substance for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animal, may be regulated so that the quantity of drug which is released at a particular time or a particular site is enhanced.

Heretofore, a variety of techniques have bene used to provide protective coverings for druge so as to impart sustained release or controlled release or to make oral administration more palatable or even feasible. These prior art pharmaceutical prepartion methods include encapsulating the drug, coating granules or tablets of drugs with films of suitable materials, combining the drug with an ion exchange resin, chemically combining a basic drug in an acidic polymer gel or physically entrapping the drug in a polymer matrix. The very variety of available processes itself illustrates both the range of problems posed in formulating pharmaceutically active materials and the need for improved processes offering greater control, flexibility and economy.

Many drugs used in oral liquid dosage forms, such as cough preparations, including solutions, syrups, or suspensions, are absorbed at an uncontrolled, non-optional rate in the human system and the administration is made difficult, unpleasant, and potentially more dangerous than is necessary. The incidence of undesirable side effects such as nausea, dizziness, visual disturbances or profuse sweating accompany many drugs, particularly when rapid adsorption produces high peak blood levels which touch the toxic range. With such oral preparations, some drugs produce a bitter taste or numbing of the tongue and surrounding mucous membranes. These side effects make these prior oral pharmaceutical preparations very unpalatable, unpleasant, occasionally toxic and more hazardous than necessary. By inhibiting release or by providing gradual release of the drug at absorption sites, (a) undesirable peaking of blood levels is reduced and drug safety may be improved, (b) drug dissolution may be retarded until the drug has passed sites of high acidity where the drug is more prone to decomposition, (c) drug release may be retarded to avoid irritation in the stomach, or an emetic effect due to drug dissolution in the stomach, or (d) drug release may be delayed to make the drug available at desirable sites of absorption at a high drug concentration for improved absorption.

The compositions of the present invention help to alleviate problems and difficulties associated with prior art compositions by releasing the drug in a controlled manner so that it may have, for example, sustained, enteric slowed or delayed effect. The compositions of the invention, may be less expensively produced than many of the compositions of the prior art; the necessity for expensive coating apparatus and skilled coating personnel being eliminated. The methods of the invention permit their application to all drugs having basic or acidic group in the drug moiety.

Moreover, the invention is adaptable to use of what is known in the art as "bridging moieties" to promote sorption of cationic drug moieties and to facilitate sorption of anionic or amphoteric drugs. Pharmaceutical compositions prepared in accordance with the present invention are adapted for oral administration in any of the conventional solid or liquid oral dosage forms, for example as tablets, capsules, powder or as a suspension of powders in a

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liquid vehicle. The method of the invention is particularly suitable in preparing accurate dosage units of highly potent drugs, since the methods are characterised by their molecular or ionic scale sorption-mixability capability.

According to the invention there is provided a controlled release, orally administrable pharmaceutical composition comprising a drug having acid or basic functionality chemisorbed to latex particles of a physiologically harmless polymer that is hydratable in the gastro-intestinal tract, and has acid or basic functionality complementary to the functionality of the drug, and at least one physiologically harmless carboxylic acid chemisorbed with the drug to the latext particles, the composition exhibiting more prolonged release at a buffered pH of 4.5 than a corresponding composition free of the acid.

In the process of the invention an aqueous latex of a polymer having acidic and/or basic groups is contacted with a drug having basic and/or acidic groups in the presence of a carboxylic acid. In a preferred embodiment, the water is then removed and the product formulated into a suitable dosage form.

Although the Applicants do not wish to be bound by theoretical supposition, it is believed that the drug molecules are chemically or physico-chemically bonded to the polymer chains; in addition, the extremely high surface area presented by the polymer due to the colloidal size of the polymer particles may result in adsorption of drug molecules on the surface of the polymer particles. Carboxylic acids appear to promote sorption of drug during the process by which the drug is trapped, as well as to provide a further mechanism by which subsequent drug release may be controlled. The acids may act as counter or protective ions, retarding polymer flocculation or coagulation and/or as "bridging moieties", facilitating surface sorption of drug to polymer.

As stated, the polymers used in the invention are in an aqueous latex. By "latex" is meant an aqueous dispersion of colloidal or near colloidal polymer particles. Conventionally a polymer latex is produced by emulsion polymerization and will have particle sizes in the micron and submicron range. Minor amounts of organic liquids, such as lower alkanols, which do not interfere with the polymer-drug reaction may be present during the reaction. The functionality of the polymer and drug must be complementary. Thus, if the polymer contains both basic and acidic groups, it may be used to react with basic drugs or acidic drugs, and if the drug is both acidic and basic, the polymer may be either basic or acidic. However, where the polymer contains only acidic groups, the drug must contain basic groups for chemisorption to occur although limited physical adsorption may exist. Similarly, where the polymer is basic, the drug should be acidic except that where the added carboxylic acid is a polycarboxylic acid, this will supply, *in situ*, the complementary functionality so that both the polymer and drug can be fundamentally basic.

As an additional means of controlling drug release, drugs either may be entrapped in the presence of a soluble diluent component, or the soluble diluent may be added later in milling the dry polymer-drug product with the soluble component serving to facilitate and accelerate subsequent drug dissolution release. Suitable excipients include, for example, mannitol, lactose, urea, sorbitol, polyoxyethylene glycols and sodium chloride.

The methods of the invention may be highly reproducible, stoichiometric techniques for drug entrapment in which the level of entrapment, as well as the uniformity and degree of drug dispersion, may approach or may equal molecular scale.

The polymers useful in the invention are widely available commercially. Generally, these polymers are produced by conventional emulsion polymerization and contain one or more mers having either basic or acidic groups. Suitable acidic groups include for example carboxylate, sulfonate, and phosphonate. Suitable monomers embodying these acidic radicals include acrylic acid, methacrylic acid, crotonic acid, itaconic acid, maleic acid, half-esters of maleic acid, maleic anhydride, sulfonated styrene and phosphonated styrene. Suitable monomers containing basic functionality include for example vinyl amine, the aminoalkyl esters of any of the aforesaid acids such as aminoethyl methacrylate. These monomers may be copolymerized with ay other copolymerizable monomer so long as the resulting polymer does not produce any adverse physiological reaction. Polymers useful in the invention include for example, those produced by copolymerizing one or more of the above acidic or basic monomers with vinyl acetate, vinyl propionate, vinyl ethers, hydroxyethyl methacrylate, acrylonitrile, ethylene, styrene, vinyl chloride and one or more alkyl acrylate or methacrylate monomers.

The maximum amount of acid in the copolymer is determined by the solubility characteristics of the overall copolymer composition, i.e., above a certain acid level it is not possible to form a latex. This level varies with the nature of the acid and of the monomers. Thus, methacrylic acid could be present in up to about 75% by weight when copolymerized with other monomers of median hydrophobic properties such as the lower alkyl esters of acrylic and methacrylic acid, while slightly more acid could be used if the other monomers were strongly hydrophobic, such as styrene. Conversely, the maximum acid level would be lower for acids which are more strongly hydrophilic than methacrylic acid,

such as maleic acid or acrylic acid. The presence of nonionic hydrophilic groups, such as ether linkages or hydroxy groups, will also act to lower the maximum acid level.

The minimum acid level in the copolymer is determined both by the ability of the polymer to entrap a reasonable amount of drug and by the ability of the polymer to be hydrated, e.g., swelled or even dissolved by digestive fluids either in the stomach (acid pH) or the small intestine (slightly basic pH). The swelling need not be great. The polymer contains sufficient acid content if a dried powder produced from the polymer approximately doubles in size in stomach or intestinal fluid at 37°C. This actions assists the dispersion of the drug making it available to the body more readily than would be the case if the polymer were inert to the digestive fluid. This is important in the polymer-drug products of the invention due to the molecular scale of entrapment as opposed to the channels of drug created when dry polymer and drug are mixed and tabletted. Again the minimum amount of acid will vary with the nature of the acid and of the other monomers. Thus, for copolymers of methacrylic acid with monomers of median hydrophobic properties as defined above, about 10% acid is suitably present. More hydrophobic comonomers would require a higher acid content, while more hydrophilic comonomers (such as non-ionic solubilizing groups) or more hydrophilic acids (acrylic, maleic, etc.) would permit the use of lower acid contents.

The preferred latices found useful in the practice of the invention are polymer products made by an emulsion process which are colloidal dispersions of polymer, and are usually marketed as 20 to 60% solid dispersions, by weight. The latices of dispersed colloid of the polymer emulsions useful in the practice of the invention present a highly concentrated dispersed polymer system of high molecular weight material, which is impossible to match in high concentration in solution due to solubility and viscosity limitations. For example, it has been estimated that such a typical polymer emulsion contains in the order of 10^{14} or 100 trillion polymer particles per cubic centimeter of dispersion.

Because of their ready commercial availability and suitable physical form, it is preferred to use polymers produced by emulsion polymerization. Polymer dispersions produced by alternate processes may be used. For example, copolymers may be produced by non-aqueous dispersion polymerization, the organic phase then being replaced with water. These and other polymerization techniques are well known to those skilled in the art and do not constitute the invention.

The invention is applicable to all classes of drugs having acidic and/or basic groups. Where the drug contains a basic nitrogen group, the drug may be used in the invention either as the free amine or as a salt as, for example, a hydrochloride or sulfate.

Basic drugs include, for example, dextroamphetamine, racemic amphetamine, d-desoxyephedrin, chlorpromazine, prochlorperazine, trifluoperazine, methapyrilene, diphenylhydramine, chlorprophenpyramidamine, chlorpheniramine, codeine, atropine, reserpine, strychnine, phenylephrine, phenazocine, pilocarpine, morphine, homatropine, ephedrine, dihydrocodeinone, pyrilamine and the like. Amphoteric drugs may also be used and include, for example, penicillins and their salts, cephalosporins and their salts and derivatives. Acidic drugs useful in the invention include, for example, the barbiturates and aspirin.

The great majority of drugs—perhaps as many as 90%—contain basic functionality. Accordingly, the invention will be described in terms of a basic drug and an acidic polymer, but it should be understood that it is equally applicable to a basic polymer with an acidic drug, or, in certain circumstances, with a basic drug and a basic polymer as described above.

The acids useful in the invention comprise monocarboxylic acids as well as polycarboxylic acids provided they are sufficiently soluble in the reaction system, e.g. have sufficient solubility, to form salts with the drugs when the latter are basic. Even acids which are only slightly water-soluble can be used since as dissolved acid is used up in the reaction, more will go into solution. Typical useful monocarboxylic acids are acetic acid and aminoacetic acid (glycine). Useful polycarboxylic acids include saturated aliphatic acids such as oxalic acid, malonic acid, succinic acid, glutaric acid and adipic acid; unsaturated aliphatic acids such as maleic acid and fumaric acid; hydroxy acids such as citric acid and tartaric acid; acids of a more complex functionality such as ascorbic acid; and carbocyclic acids such as the phthalic acids.

The carboxylic acid additives can be added directly to the polymer-drug system or can be added as a carboxylate. Thus, the acid can be mixed with a solution of drug hydrochloride salt and polymer added thereto and flocculated. Alternatively, the acid can be added to a solution of the drug and reacted therewith, and the drug-acid carboxylate crystallized from solution; typically, the carboxylates are recrystallized from one to three times from an isopropanol/ether solution, and vacuum dried. The crystallized carboxylates are then mixed in solution with the polymers for the sorption-flocculation step. In general, the acid and drug are mixed and/or reacted in approximately equimolar concentrations (as in the examples, unless otherwise indicated). However, the carboxylic acid, e.g., a dicarboxylic acid, may be added in less than equimolar concentration but the resulting sorption increase will be something less than the possible maximum,

albeit, greater than if no carboxylic acid were utilized.

The choice of a process by which the drug, acid and polymer are contacted to interact to produce the sustained release, delayed release, controlled release or enteric final composition is highly flexible and includes pipeline mixing, countercurrent mixing of opposing fluid streams, jet-stream mixing (i.e., jet stream injection of one liquid phase into the other or a countercurrent stream of the other), tank mixing, or any related fluid mixing operation. Also it has been found that whether such mixing is high shear or low shear, during the sorption and trapping process, and whether the rate of admixture of one component with the other is high or low, has little general effect on the sorption and entrapment process. Where maximum drug sorption is desirable, it has been found advisable to add the drug and acid in solution to the polymer emulsion. It is not essential for the drug or drug salt to be completely soluble in the aqueous phase, but only to furnish a higher concentration of ions than the polymer-drug reaction product. Where the drug or drug salt is only partly soluble, the ions in solution react with the polymer. As the reaction removes ions from solution, additional drug dissolves until the reaction is complete. The drug and polymer need not be reacted in stoichiometric proportions. Thus an amount of drug over and above that which can react with the polymer may be used. The presence of such a drug fraction in compositions of the present invention, which is physically and mechanically entrapped, i.e., which is not chemisorbed to the polymer, and which is not, in general, involved in the ionic charge dissipation of the polymer emulsion to bring about coagulation of the emulsion, may be utilized to:

1. Increase the overall rate of drug release, if such physicaly and mechanically entrapped drug has good solubility properties in the upper gastro-intestinal tract,
2. Decrease the overall rate of drug release from the final composition, if the mechanically entrapped fraction does not have good solubility properties in the upper gastro-intestinal tract, or,
3. Permit use of a drug which is in a form which can only be mechanically entrapped to be combined in this process along with the same or a different drug which can be molecularly trapped, to increase the overall drug concentration of the final composition to above 60%, which is the usual upper limit of drug concentration which can be obtained by molecular scale sorption of drug from a solution, or to permit useful combinations of drugs, each with its own designed controlled release rate.

The addition of a drug or drug salt which is not in solution or which cannot go into solution readily in the polymer emulsion or in a solvent which is miscible with the polymer emulsion and which cannot be trapped other than by mechanical means is not usually a primary goal of this invention, since such entrapment would be less uniform and reliable than the main feature of this invention, i.e., molecular to ionic scale drug sorption from solution. However, the combination of molecular scale drug sorption and gross physical scale entrapment may also be employed in the practice of the present invention.

In one preferred embodiment of the invention, the drug is added to a considerable excess of the polymer. Certain drugs must be administered in highly accurate unit doses each containing only a few micrograms of drug. Too little of such a drug in each dose unit might result in failure to treat the disease while an excess of drug over the desired amount may lead to a greater incidence of unwanted side effects or to direct acute toxicity. Also where the difference between an effective dose and a toxic dose is slight, extreme precision in formulation is essential. Present techniques of mechanically blending finely ground powders obviously present problems in accurately controlling the level of active ingredient in each unit dose. Variables include the particle size to which the drug has been reduced, the relative particle size distributions of drug and polymer and the uniformity of particle-particle mixing. The present invention can permit easy and precise control of drug dispersion and much more uniform drug distribution which is predicated on physico-chemical principles rather than mechanical factors. This may be accomplished by contacting an aqueous solution of the drug and acid with a considerable excess of polymer. The drug, being in solution, will be distributed throughout the emulsion as separate molecules or ions which statistically will be randomly distributed throughout the polymer. Thus, instead of dividing one gram of drug into 100,000 approximately equal particles by fine milling, the present invention can permit highly uniform distribution of the drug as 6×10^{23} molecules/mole throughout the polymer, e.g., at a level of one gram of drug per kilogram of polymer, thus simplifying the problem for the formulator, greatly improving the reliability of mixing, and reducing the mass of dispersed drug by many orders of magnitude. A typical drug with a molecular weight of 300 would produce 2×10^{21} molecules or ions for every gram in solution as compared to 1×10^{5} to 1×10^{7} milled particles per gram.

As previously stated, the drug may most commonly be entrapped at a molecular scale level when combined with the polymer emulsion as an aqueous or primarily aqueous solution of the drug salt. However, in some cases, it may be more convenient to combine the drug

in its free base or acid non-salt form and the free carboxylic acid with the polymer emulsion, the free base being added as an aqueous solution, organic solvent solution or aqueous dispersion. If the drug base is slightly soluble, as is phenylpropanolamine, the drug as an aqueous solution may be combined with the polymer emulsion. Most cationic drugs in free base form or anionic drugs in acid form are water insoluble, and may be added to the polymer emulsion directly as the oily liquid or insoluble powder free base or acid form, or as a dispersion of the free base or acid in an aqueous medium, or as a solution of the free base or acid in an organic solvent which does not interfere with the drug-polymer reaction. As previously described, the most advantageous form of addition is frequently for the drug to be in its maximally disposed form, i.e., in solution.

Since the pH of the most physically stable polymer emulsions containing a polymer with an acidic functional group is acidic, a drug base which is combined with such polymer emulsions will be converted, at least in part, to the drug salt form, (ionized species), and will be indistinguishable, as to process result or final composition characteristics, from the process of final composition characteristics of adding the drug salt initially in solution. Of course, it will be appreciated that substantial conversion of the drug base to the ionized species must occur before coagulation of the polymer dispersion is completed.

The aqueous solution of dispersion produced by contacting the drug and polymer as described may be used as such for formulating a pharmaceutical composition, for example by adjusting the pH or adding coloring and/or flavoring agents. It is preferred, however, to separate the reaction product from the liquid phase and then formulate the product into a tablet, powder or similar pharmaceutical composition using conventional procedures and compounding ingredients. Where the product is itself insoluble, it may be readily separated for example by filtration or centrifugation. Other procedures for separating the drug-polymer product involve coagulation as by the addition of a suitable electrolyte or polymer of suitable electric charge, followed by filtration or centrifugation; spray drying; freeze-drying or vacuum evaporation.

The techniques of addition of a non-drug electrolyte to accelerate the coagulation process may be preferably employed either where low quantity levels of drugs are being entrapped (10% or less and usually 2% or less drug in final dry polymer-drug product) which will not in and by themselves reach the requisite flocculation value of the polymer emulsion, or where complete drug sorption is not desirable due to the desire to avoid an excessively retarded drug release. The flocculation value (concentration of ion required to produce visible coagulation following some specified time interval, usually 5 or 10 minutes), for a given ion, varies widely for different anionic or cationic polymer emulsions. Factors involved include intensity of charge on the polymer colloidal particles, pH, other additives or stabilizers, temperature, agitation, addition of desolvating solvents and other effects. Likewise the quantity of different drugs required to produce coagulation of a single polymer emulsion varies widely as does the concentration of electrolyte. The first case above, addition of non-drug electrolyte to accelerate coagulation at low quantity levels of drugs, is the usual cause for adding additional non-drug electrolyte. It is noted that polyvalent cations are most effective in coagulating anionic colloids and, when used, will be present in the final composition. Electrolytes such as magnesium sulfate, sodium phosphate and aluminum chloride have been found particularly effective as coagulants in the practice of the present invention. An anionic polymer latex may also be used to coagulate a cationic polymer latex, and a cationic polymer latex to coagulate an anionic polymer latex.

If the coagulated drug-polymer system is not immediately separated from the liquid phase, in many cases only an insignificant quantity of the drug will return to the solution, i.e., become desorbed. Thus, where the reaction product was not separated from the aqueous phase for 72 hours, only a negligible quantity of drug was found to return to the aqueous phase.

The drug-sorption interaction rate between certain drugs and polymers of the present invention is rapid, equilibrium being reached within one-half hour or less at room temperature (about 20°C.). Chemisorption thus appears to occur rapidly, with subsequent desorption occurring, under flocculation conditions, very slowly, if at all, depending upon the concentration of drug and polymer.

The polymers of the polymer emulsion systems found useful in the practice of the invention exhibit hydration, as evidenced by swelling or solubility characteristics, in the physiological pH range of gastro-intestinal juices of fluids at normal body temperatures (37°C.). The solubility rate of a typical polymer exhibiting a delayed or sustained release pattern is shown in Table 1.

TABLE I

RATE OF SOLUBILITY OF LATEX A*

Total Hours Immersed	Cumulative % Dissolved	pH of Fluid
1	7.4	1.4
2	7.1	1.4
3	7.7	2.1
4	7.7	2.6
5	11.2	5.5
6	60.0	6.9
8	100.0	7.4

*Latex A is an acrylic copolymer containing about 35% carboxylic acid functionality. It is available from the Rohm and Haas Company Philadelphia under the Trademark ACRYSOL ASE—75. The latex contains 40% solids.

Temperature also does not appear to have any substantial effects on the sorption process itself. Thus the reaction between Latex A and methapyrilene proceeded with equal effectiveness at 4° and at 25°C. For convenience, the process of the invention would normally be carried out at room temperature. However, where the solubility or stability of the drug is a factor, higher or lower temperatures for example from 0°C. to 100°C. may be used as appropriate.

The drug-polymer dispersion system which is obtained from the present sorption process may conveniently be separated from the remaining bulk phase or supernatent liquid by conventional processes as described, followed by drying and milling to a granular or fine, free-flowing powder, which can readily be encapsulated or tabletted in oral dosage form or suspended in a liquid vehicle.

Any convenient drying process may be used to obtain the dry product, whether direct heat, vacuum, spray, or the like. It is noted that drying temperatures which exceed the glass point of the polymer serve to densify the polymer-drug system composition. Such densification may have the effect of retarding drug release by reducing effective total release site surfaces.

The sorption process permits efficient use of drugs adsorbed from solution. The filtrate remaining following recovery of the flocculate may be reused, with or without the incorporation of additional drug. The efficiency of utilization of drugs, following repeated flocculation of the filtrates remaining from previous flocculate separations without the incorporation of additional drug, is shown by comparative tests to be in some cases many times greater by the practice of the present invention. Thus, using maleic acid as the additive acid, the concentration of drug can be reduced from 10% to 0.3% in only two flocculations. Without the additive acid, at least three, and generally four, flocculations are required to accomplish the same drug recovery.

The addition of a non-drug electrolyte along with the drug and acid to the polymer emulsion may be preferably employed to accelerate the coagulation process, either where low quantity levels of drugs are being entrapped (10% or less and usually 2% or less drug in final dry polymer-drug product) which will not in and by themselves reach the requisite flocculation value of the polymer emulsion, or where complete drug sorption is not desirable due to the desire to avoid an excessively retarded drug release. Polyvalent cations are most effective in coagulating anionic colloids (Schultz-Hardy Rule) and when used, will, thus, be present in the final composition in a low concentration as a contaminant. Electrolytes, such as magnesium sulfate, sodium phosphate, and sodium chloride, have been found particularly effective for this purpose in the practice of the present invention.

Preferred embodiments of the invention will now be more particularly described, for the purposes of illustration only, in the following Examples.

EXAMPLE 1

Aqueous drug solutions were prepared from methapyrilene salts. To 50 ml. portions were

added 50 ml. of latex A (defined previously herein) with constant stirring. The resulting mixtures were suction-filtered, the filtrates were assayed, and the amount of drug in the filtrate and flocculant were determined. The tests are summarized in Table 2.

TABLE 2

Initial Drug Solution		% Of Initial Drug In Filtrate	% Of Initial Drug In Flooccculant
Methapyrilene HCL	0.07 Molar	45.8	54.2
Methapyrilene HCL Succinic Acid	0.08 Molar 0.08 Molar	36	64
Methapyrilene HCL Succinic Acid NaOH	0.08 Molar 0.08 Molar 0.08 Molar	9	91
Methapyrilene Succinate	0.08 Molar	9	91

The effect of the dicarboxylic acid or of the dicarboxylate drug salt on the concentration of drug entrapped by the polymer in the presence of the dicarboxylate or dicarboxylic acid compound is apparent. Only about 54% of the drug in the 0.07 Molar drug hydrochloride solution was sorbed and swept from solution, while over 90% of the drug carboxylate (succinate) was sorbed under the same conditions, except at a higher drug solution concentration (0.08 Molar vs. 0.07 Molar). It should be recognized that the proportion of the initial drug found in the flocculant generally decreases with an increase in the initial drug concentration.

EXAMPLE 2

Following the foregoing procedures, 100 ml. of drug solution were added to 100 ml. of polymer emulsion, the flocculated mass was mixed for 30 minutes at room temperature, and this was followed by vacuum-aided filtration and drying.

Table 3 data shows clearly the chemical affinity between the carboxylic acid drug salts and the polymer, since 80 to 90% of the carboxylic acid salts were removed from the drug solution while only about 50% of the hydrochloride salt was removed by the flocculation process. The succinate salt had a remarkable affinity for the polymer, and was entrapped with less than 2% loss in the case of the 2% drug solution. The adipate salt as a 2% drug solution failed to flocculate the polymer without employing an added electrolyte, e.g., 5% Mg SO_4 and the concentration of chlorpheniramine adipate was therefore increased to 5%.

TABLE 3

EFFECT OF ACID ANION, UPON THE SORPTION OF CHLORPHENIRAMINE BY ACRYSOL ASE—75

Acid Anion Moiety	Initial Conc. of Drug Soln. % w/v	% of Initial Drug Sorbed	% Drug in Dry Flocculant
Hydrochloride	2	54	3.3
Maleate	2	91	3.7
Oxalate	2	80	3.7
Malonate	2	90	3.9
Succinate	2	98	4.5
Succinate	5	93	10.0
Succinate	10	86	17.5
Adipate	5	96	10.4

EXAMPLE 3

To show the effect of drug salt form and drug concentration, several different drug-acid salt combinations were prepared and flocculated with polymer (Acrysol ASE—75) as described previously. These were then tested for release rate by placing 5 Gm. of polymer-drug material in 50 ml. of fluid in a 3 oz. round bottle, which was rotated at 37° for the times specified, prior to assay. The release characteristics are shown in Table 4. In the table, "S.G.F." refers to simulated gastric fluid U.S.P., with enzyme omitted; "Buffer" refers to U.S.P. phosphate buffer, pH 4.5; and "S.I.F." refers to simulated intestinal fluid U.S.P., with enzyme omitted.

TABLE 4

Drug Salt Form and Concentration	Suspension Media	% Drug Released in Hours 24 Hrs.	48 Hrs.	120 Hrs.	Final Suspension pH
Chlorpheniramine Salts					
Succinate 4.3%	S.G.F.	57	62	69	1.4
	Buffer	3	3	3	4.1
	S.I.F.	99	97		7.1
Succinate 10%	S.G.F.	86	84	84	1.4
	Buffer	12	12	12	4.5
	S.I.F.	91	97		7.4
Succinate 18.9%	S.G.F.	81	83	85	1.4
	Buffer	18	19	21	4.9
	S.I.F.	89	94		8.0
Hydrochloride 3.5%	S.G.F.	38	36	38	1.4
	Buffer	8	8	9	3.2
	S.I.F.	66	74		6.9
Oxalate 4.3%	S.G.F.	50	56	56	1.4
	Buffer	6	6	6	3.8
	S.I.F.	86	92		7.0
Malonate 4.1%	S.G.F.	62	67	68	1.4
	Buffer	5	5	5	3.6
	S.I.F.	88	98		7.0
Maleate 3.9%	S.G.F.	55	58	67	1.4
	Buffer	5	6	6	3.9
	S.I.F.	91	100		7.0
Adipate	S.G.F.	82	81	85	1.4
	Buffer	10	10	10	4.4
	S.I.F.	92	95		7.7
Methapyrilene salts					
Hydrochloride 3.2%	S.G.F.	56		65	1.8
	Buffer	7		7	4.0
Fumarate 2.5%	S.G.F.	46		62	1.7
	Buffer	10		8	3.6
Succinate 3.3%	S.G.F.	64		65	1.8
	Buffer	5		3	4.3

The relationship between drug release and drug concentration in the polymer-drug system is clearly shown by the three chlorpheniramine succinate systems in the phosphate buffer. Ordinarily polymer-drug systems would not be prepared containing more than 10% of an antihistamine drug, based on the dose of such drugs. The release data of carboxylic acid drug salts correspond closely to the entrapment data and to the probable order of drug salt affinity for the polymer. The degree of release may be arranged as follows: Adipate, Succinate, Malonate, Maleate, Oxalate and Hydrochloride.

The dialysis release of the polymer-drug system of Acrysol ASE—75 was investigated to determine whether drug would be permanently bound to the polymer. The polymer *per se* did not dialyze through the semi-permeable membrane employed, but the drug did freely dialyze. The dialysis release of the polymer-drug entrapment system was then determined, and thed rug was observed to be from 87% to 98% available for dialysis. In other words,

equilibrium dialysis analysis indicated that as little as 2% of the entrapped drug, and not more than 13% of the drug is permanently bound by the polymer, and would be unavailable for absorption. Thus, for example, a chlorpheniramine maleate-polymer system releases drug at a substantially slower rate in gastric juice than the hydrochloride system even though the maleate drug salt and hydrochloride drug salt may have nearly identical aqueous solubility properties, the concentration of maleate drug salt in the entrapment matrix is higher, and a smaller sample can be used in the release determination. All these factors should cause a more rapid release of chlorpheniramine maleate. The slower release of the chlorpheniramine salt is the result of polymer-drug interaction, which is less pronounced or non-existant in the case of the hydrochloride.

The dialytic release rates in intestinal fluid are higher for the maleate than for the hydrochloride, but this data is difficult to interpret due to the solubilization of the polymer at the pH of intestinal fluid. The dissolved polymer produces a very viscous solution in the dialysis sacs and probably also tends to block the pores of the membrane.

The effect of the polymer-drug ratio on dialytic release rates is also significant. A chlorpheniramine maleate-polymer product, containing 96.7% polymer and only 3.3% drug, releases only a fraction of the drug after 24 hours that is released by a 16.7% drug product. The polymer-drug ratio appears to be a very useful variable to alter drug release rates.

The dialysis tests illustrate the substantially complete drug availability which can be obtained from this invention. Permanent drug binding which would prevent the drug from being available to the body would be undesirable since the drug dosage would have decreased effectiveness.

Example 4

To further demonstrate the release of chlorpheniramine maleate from polymer, 5.0 Gm. of chlorpheniramine maleate-Acrysol ASE—75 flocculate product, containing 3.7% drug, as a 60 mesh undersize powder, was suspended in 100 ml. of vehicle in a 4 oz. reagent bottle. The bottles were shaken vigorously initially and once each day over the test period. The results of the periodically assayed products are given in Table 5. The data indicates premature drug leach-out in liquid vehicles is controllable and liquid suspension sustained release products are feasible.

Table 5

Release of Chlorpheniramine Maleate from an Acrysol Matrix in Various Buffers and Vehicles

Vehicle	pH of freshly prepared Suspension	Cumulative % Drug Release in Days			
		2	7—8	14—15	30
Phosphate Buffer, pH 4.5	4.3	2.4	2.5	2.3	3.6
Phosphate Buffer, pH 6.0	5.6	0	3.8	4.2	3.6
Phosphate Buffer, pH 8.0	6.1	32.3	42.4	45.3	60.0
Orange Syrup U.S.P.	2.4	1.6	2.0	2.4	2.7
1% Citric Acid Solution	2.3	11.7	23.1	27.0	35.4
Distilled Water — continuously stirred for 30 days with magnetic stirrer	3.3	6.4	7.1	7.5	9.6
Distilled Water	3.3	4.6	6.2	6.8	7.0
Standard Soln. 200 mg. dry drug-maleate per 100 ml. of water	4.5	100	100	100	100

As is shown, drug release is retarded between pHs of about 2.5 and 5.6 to 6. Continuous stirring of a distilled water suspension over a 30 day period produced no increased release over a similar suspension which was only shaken daily. Release thus is a controllable factor.

EXAMPLE 5

Sorption of an antihistamine dicarboxylic acid drug salt

In a further example, 2 gm. of chlorpheniramine succinate is mixed in 50 ml. of water and stirred constantly. To this mixture is added 50 ml. of an acrylic-acrylate copolymer emulsion (Acrysol ASE—75)—(a carboxyl to ester ratio of about 2:5) over a 10 minute period at room temperature. The flocculated mixture is then stirred for approximately 30 minutes, filtered with suction and dried. The dried flocculate and filtrate were then assayed for drug content. It was found that the amount of drug in the filtrate (not entrapped) was 1.7% and the amount of drug in the flocculant (entrapped) was 98.3% of that originally present. The product may be encapsulated or directly tableted to produce a sustained release product, or suspended for a liquid product.

EXAMPLE 6

Sorption of a drug hydrochloride in the presence of a dicarboxylic acid and an equimolar quantity of base

Ingredients	Amount
Phenylephrine hydrochloride	5.0 gram
Maleic acid	1.6 gram
Sodium hydroxide	1.0 gram
Distilled water	50.0 ml.
Neocryl BT4—(Anionic Acrylic Copolymer emulsion)	50.0 ml.

The phenylephrine, maleic acid and sodium hydroxide are dissolved in 50 ml. of water at 25°, and added slowly (within about one-half minute) with constant stirring to the polymer emulsion (also at 25°), Neocryl BT4. The resulting product is filtered and dried. The presence of the sodium hydroxide is to promote solubility and ionization of the dicarboxylic acid in the drug solution. The product can be made into a sustained release suspension in the following manner:

Ingredients	Amount	
Phenylephrine product	1.00	gm.
Glycerin	10.00	ml.
Sodium Carboxymethylcellulose	2.00	gm.
Methyl paraben	0.0625	gm.
Propyl paraben	0.0125	gm.
Sugar syrup, USP	50.0	ml.
Imitation cola flavor	0.1	ml.
Soluble lemon-lime flavor	0.03	ml.
Purified water, USP q.s.	100.00	ml.

The parabens are dissolved in the glycerin with the aid of heat and the sodium carboxymethylcellulose added to the glycerin solution. The glycerin mixture is then added to a water-syrup-phenylephrine mixture and stirred until evenly suspended. The flavors are added and the suspension brought to the desired volume by addition of sufficient water.

EXAMPLE 7

Sorption of drug hydrochloride in the presence of monocarboxylic acid

Ingredients	Amount
Phenylpropanolamine Hydrochloride	20.0 gm.
Acetic Acid	Equimolar Quantity
Purified Water U.S.P.	100.0 ml.
Acrysol ASE 75	100.0 ml.

The drug is dissolved in the water at room temperature (25°), the acid added and this solution rapidly combined (poured directly together within 15—20 seconds) with the polymer emulsion, also at 25°, with stirring. The resulting flocculate is suction filtered and oven dried at 37°C. The resulting product contained 9.7% drug and provided a sustained release in man corresponding to a biological half life determined by urinary excretion, averaging 8.5 hours. The average biological half-life of the control, i.e., non-entrapped, unmodified U.S.P. drug hydrochloride was 4.7 hours.

EXAMPLE 8

Data for a straight non-dialytic solubility release of a chlorpheniramine maleate-polymer system were obtained as a function of particle size. Half gram samples of each polymer-drug particle size fraction were placed in either 50 ml. of gastric or 50 ml. of intestinal fluid, and were rotated and assayed at the times specified. Table 6 illustrates that the particle size has little effect on release rate.

TABLE 6

EQUILIBRIUM SOLUBILITY RELEASE OF CHLORPHENIRAMINE MALEATE FROM AN ACRYSOL ASE—75 FLOCCULANT SYSTEM (4.1% DRUG) IN TEST MEDIA AS A FUNCTION OF PARTICLE SIZE

Particle Size (Sieve Fraction)	% Drug Released in 24 Hours at pH 1.2	at pH 7.4	% Released in 96 Hours at pH of 1.2
30 Mesh oversize	62	91.5	67
30/40 Mesh	65	92.0	70
40/60	67	91.0	72
60/120	69	92.5	75
120/170	71	90.5	75
170/230	75	92.5	80
230 Undersize	77	91.0	80

Even though there is a promoted sorption, binding and entrapment of the carboxylic acid drug salt by the polymer, 90% or more of the drug was available in intestinal fluid in the in-vitro test, and particle size had a small effect on equilibrium solubility of the sieve fractions in gastric media, but not in intestinal media.

EXAMPLE 9

Entrapment of a soluble and an insoluble salt form of the same drug

Ingredients	Amount
Chlorpheniramine Pamoate (insoluble Salt)	2.0 Gm.
Chlorpheniramine Succinate (Soluble Salt)	2.0 Gm.
Water, Purified	100.0 Ml.
Neocryl BT4 Charge	100.0 Ml.

Product	% Solids	% COOH on Solids
Acrysol ASE 60	27.7	21
Acrysol 108	20.0	36

(Products of Rohm and Haas Co.)

Disperse the pamoate salt in the polymer emulsion, dissolve the succinate salt in the water, and add the polymer emulsion slowly to the aqueous solution with stirring. Separate the coagulated material by filtration, dry and grind to size. The chlorpheniramine pamoate is mechanically and grossly entrapped; the chlorpheniramine succinate is ionic to molecular scale entrapped. The release rate (dissolution release rate) in gastric fluid of the resulting product is between 33% and 50% slower than that observed in the polymer drug product containing only the soluble chlorpheniramine succinate salt at the same concentration level.

Polymer emulsions in cross-linked form are also commercially available—some of which contain residual COOH groups. Examples:

Socalled self-crosslinking polymers such as X—Link 2802, sold by National Starch and Chem. Corp., N.Y., N.Y., are also commercially available—which have been found useful in the practice of the present invention. Use of such materials is ilustrated by the following example.

EXAMPLE 10

Ingredients	Amount
Pyrilamine Maleate	100 Gm.
Magnesium Sulfate	50 Gm.
Purified Water	750 ml.
Acrysol ASE—60 (Modified acrylic, partially cross-linked, polymer emulsion containing anionic surfactant, 28% w/w solids, pH 3.5, Rohm and Haas Co.).	2000 ml.

Dissolve the first two ingredients in the water, add slowly with stirring to the polymer emulsion, separate, dry and mill.

In the following examples, all of the component except the polymer are first dissolved in water, the resulting solution is added slowly

with stirring to the polymer emulsion, and the flocculate is separated by vacuum filtering, dried at 50°C. and milled to size.

EXAMPLE 11

Ingredients	Amount
Atropine Sulfate	10 Gm.
Malonic Acid	20 Gm.
Magnesium Sulfate	15 Gm.
Distilled Water	200 ml.
Acrysol ASE 95 (Modified acrylic polymer emulsion, 20% solids w/w, pH 3.0, Rohm and Haas Co.).	500 ml.

EXAMPLE 12

Sorption of an amphoteric drug (hydrochloride salt form) facilitated by dicarboxylic acid employing polymer emulsion

Ingredients	Amount
Oxytetracycline Hydrochloride	250 Gm.
Succinic Acid	120 Gm.
Sodium Hydroxide	40 Gm.
Water	2000 ml.
Emulsion 4—E J S—35 (An polymer emulsion containing anionic surfactant composed of ethyl acrylate and acrylic acid in a 60:40 ratio).	2000 ml.

EXAMPLE 13

Sorption of an amphoteric drug (sodium salt form) facilitated by a dicarboxylic acid employing a polymer emulsion

Ingredients	Amount
Oxytetracycline Disodium Salt Dihydrate	100 Gm.
Maleic Acid	50 Gm.
Water	600 ml.
Acri-Flo 150 (A styrene-acrylic polymer emulsion containing a non-ionic surfactant, Chemical Division of General Tire and Rubber Co., Akron, Ohio).	

EXAMPLE 14

Sorption of anionic drug by a polymer with the aid of a di-functional cation

Ingredients	Amount
Phenobarbital	150 Gm.
Aminoacetic acid	50 Gm.
Purified Water	800 ml.
Rhoplex AC—200 (Modified acrylic, polymer emulsion containing a non-ionic surfactant, 46% solids, w/w, pH 9—10).	1000 ml.

In a series of *in vivo* tests on human subjects, the phenylpropanolamine acetate-polymer product of Example 7 was utilized and compared with U.S.P. phenylpropanolamine suspended in simple syrup. The effective drug dosage was 50 mg. in each instance. The duration of effectiveness for the drug-polymer product was almost twice that of the U.S.P. drug, with an average urinary excretion half time of 8 hours for the former as compared to 4—3/4 hours for the latter. Additionally, substantially more variations in drug availability and elimination was observed with the U.S.P. drug.

Tabletting the polymer-drug product reduces release rates, provides an additional means of controlling release, and permits the use of higher drug concentrations while retaining satisfactory release rates. The dissolution of the resultant tablets can be made to occur at various time intervals; with excellent uniformity in percent of hourly drug release.

As exemplified, drug release in a gastric environment can also be controlled by the use of a combination of soluble and insoluble drug salts. To reduce the percentage of drug released in gastric contents a higher ratio of insoluble to soluble drug salt may be employed. All of the drug will be physiologically available in the intestinal environment due to the gradual but complete solubility of the polymer in that environment.

In the preferred product of the invention, the carboxylic acid-drug combination is evenly distributed throughout the polymer matrix, the drug remained associated to the polymer without alteration after high speed milling in a comminutor, and is contained in the various particle size fractions in the same concentration. This is a further advantage of the invention and suggests other applications for the invention. Polymer matrices used as diluents permit the preparation of drug or other active ingredient dilutions, in a level of uniformity not achievable in standard powder mixtures. The various particle size fractions of the entrapped active ingredient-polymer systems may be identical in percentage composition of the active ingredient. This is not usually the case for standard powder dilutions, where it is a rule of powder mixing technology that the active ingredient and excipient diluent have approximately the same particle size. Even this does not ensure a uniform powder dilution since surface charges, electrostatic effects or other physico-chemical phenomena may prevent the preparation of uniform distribution powder dilutions. These problems can be avoided when this invention is used to provide molecular to ionic scale dispersion (not possible in powder mixtures) of active ingredients throughout a polymeric vehicle.

By the present invention, drug may be present in the resulting dried polymer flocculant in amounts of from 0.5%, or less, to 60%. No lower limit has been found by the Applicants for the level of drug concentration which may be uniformly sorbed based on the molecular-to-ionic-scale drug sorption. Levels of drug concentration of 0.001% and less have been

uniformly and successfully sorbed, with or without coagulation of the polymer colloid being employed to extract the polymer. At levels of drug concentration below about 3 to 10% in the dry polymer-drug system, it is possible, depending on the flocculation value of the drug and on the stability of the polymer colloid, to sorb drug without flocculating the system. To obtain a dry polymer-drug system, in such cases, ultracentrifugation, freezing or other mechanical means may be used to separate the polymer from the bulk phase, followed by drying.

It will be recognised from the examples and discussion that the polyfunctional acids, e.g., glycine, adipic acid, and the like, and particularly the polycarboxylic acids, e.g., succinic acid, etc., are preferred. These are capable of serving both as protective electrolytes and as bridging anions in improving the pharmaceutical products. The monofunctional acids, e.g., acetic acid, while providing improvement, are not able to provide the bridging effect which contributes so significantly to the present invention.

Reference is hereby made to my copending Application Number 43480/69 (Serial No. 1278817).

WHAT I CLAIM IS:—

1. A controlled release, orally administrable pharmaceutical composition comprising a drug having acid or basic functionality chemisorbed to latex particles of a physiologically harmless polymer that is hydratable in the gastro-intestinal tract and has acid or basic functionality complementary to the functionality of the drug, and at least one physiologically harmless carboxylic acid chemisorbed with the drug to the latex particles, the composition exhibiting more prolonged release at a buffered pH of 4.5 than a corresponding composition free of the acid.

2. A composition as claimed in Claim 1 wherein the acid contains at least one amino and/or hydroxy group.

3. A composition as claimed in Claim 1 or 2 wherein the acid is a polycarboxylic acid.

4. A composition as claimed in any preceding Claim, wherein the acid is a water soluble, aliphatic dicarboxylic acid.

5. A composition as claimed in any preceding Claim, wherein the polymer is an acrylic polymer having acid functionality and the drug is a basic drug containing at least one basic nitrogen-containing group.

6. A composition as claimed in any preceding Claim, wherein the carboxylic acid is present in a substantially equimolar concentration with respect to the amount of drug.

7. A composition as claimed in any preceding Claim, wherein the polymer is an emulsion polymer containing units from (a) one or more of acrylic acid, methacrylic acid, crotonic acid, itaconic acid, maleic acid, half-esters of maleic acid, maleic anhydride, sulfonated styrene, and phosphonated styrene and (b) one or more of vinyl acetate, vinyl propionate, vinyl ether(s), hydroxyethyl methacrylate, acrylonitrile, ethylene, styrene, vinyl chloride, lower alkyl acrylates and lower alkyl methacrylates.

8. A composition as claimed in any preceding Claim, which contains drug entrapped in the polymer particles.

9. A composition as claimed in Claim 8 in which the entrapped drug differs from the chemisorbed drug.

10. A composition as claimed in any preceding Claim, in the form of a liquid suspension or a dry solid.

11. A composition as claimed in any preceding Claim in unit dosage form.

12. A composition as claimed in Claim 1 substantially as described in any one of the foregoing Examples.

13. A process for the preparation of a controlled release orally administrable pharmaceutical composition wherein a drug is sorbed on polymer particles in an aqueous latex, in the presence of a physiologically harmless carboxylic acid which is also sorbed onto the polymer.

14. A process as claimed in Claim 13, as applied to the preparation of a composition as claimed in any of Claims 2 to 11.

15. A process as claimed in Claim 13 or 14 which includes the steps of

(a) providing an aqueous latex of dispersed particles of at least one physiologically harmless polymer having acidic functionality or basic functionality or both acidic and basic functionality, the polymer being hydratable in the gastro-intestinal tract;

(b) providing a dispersion of a drug, which is at least partially soluble in the dispersing medium and has functionality complementary to the functionality of the polymer, the dispersing medium being compatible with said aqueous latex;

(c) intermixing the latex and the drug dispersion to effect sorption of said drug to said polymer particles;

(d) separating the particulate sorption product of (c); and

(e) putting the sorption product into an orally administrable form, step (c) being carried out in the presence of the carboxylic acid.

16. A process as claimed in Claim 12 substantially as described in any one of the foregoing Examples.

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